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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,097	05/06/2008	Ulrich Hersel	13907-00007-US (CPX64383P	8928

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EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
06/09/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/594,097	HERSEL ET AL.
	Examiner	Art Unit
	NISSA WESTERBERG	1618

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/8/11*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89-128* is/are pending in the application.

4a) Of the above claim(s) *94,96-98,100,103-114,117,121 and 125-128* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89-93,95,99,101,102,115,116,118-120 and 122-124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/25/06,3/9/07,7/27/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I and compound 63 in the reply filed on May 8, 2011 is acknowledged. The traversal is on the ground(s) that a search of group I will necessarily encompass the methods of group III – V, all of which depend from claim I. The compounds of group II are within the scope of the compounds of group I. The disclosure of more than one distinct species is not an appropriate basis for asserting a lack of unity.

This is not found persuasive because a lack of unity for the groups has been established by showing that the common technical feature is not a special technical feature. Applicants have not presented any arguments relevant to this point. The difference in scope between groups I and II indicates that they do not share a common technical feature and therefore a lack of unity is present.

The requirement is still deemed proper and is therefore made FINAL.

While Applicants have indicated that claims 89 - 95, 97, 98, 101, 102, 110 -113, 115 – 120 and 122 – 124 read on the elected species, the Examiner does not agree with. For examples, rHGH is not encompassed by claims 97 and 98. The claims being examined are being examined to the extent that they read on this elected species and the various values of the variables in claim 90 that define compound 63.

Comments and Notes

2. Applicants indicate that several errors are present in the published application. The Examiner doe note that the chemical formula in the specification as filed and the published version are different but is unable to take any action to correct this. Publication of applications and patents is separate from the search and examination process carried out by the Examiner. Applicants may wish to contact the Application Assistance Unit at 571-272-4200 to determine if any corrective action can be taken at this time.

Specification

3. The disclosure is objected to because of the following informalities. The specification is objected to because the method of synthesis and the structure of compound 63 are not in agreement. The “Suc” in the formula represents a succinimidopropionyl residue between the PEG polymer and the rest of the molecule. “[C]arbonate 62” is listed as a reagent, which the Examiner is assuming to be compound 62 that is coupled to the rHGH in the first step. The following steps reacts PEG-maleimide with the compound 62-rHGH compound. This reaction should result in a succinimide residue in the chain but the three carbon atoms of the propionyl portion of the structure are not found in either the maleimide-PEG or compound 62. Therefore it is not clear what the structure of the compound produced by this reaction should be.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 89 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The general formula contains “Activity Moiety” while line 4 references “the active moiety”. There is insufficient antecedent basis for the limitation “active moiety”. For the purposes of examination, the activity moiety and active moiety are assumed to be referring to the same portion of the compound.

6. Claims 89 and 91 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The preamble of the claim recites that the compound is a “polymeric cascade prodrug or corresponding linker reagent”. Nothing in claim 89 requires any polymeric component to be present in the drug. Therefore it is unclear if the preamble is meant to breathe life into the claim by reciting a structural element that must be present somewhere in the formula (e.g., when a biopolymer is the activity moiety) or if when no polymeric element is present, then the compound is deemed to be a corresponding linker reagent and no additional structure is required. Please clarify.

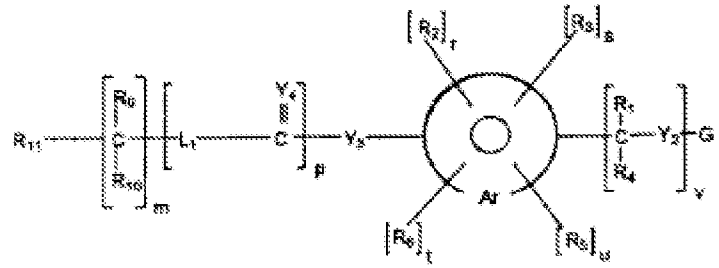
Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 89, 91 – 93 and 95 are rejected under 35 U.S.C. 102(b) as being anticipated by Greenwald et al. (WO 99/30727).

Greenwald et al. discloses double prodrugs with a polymeric portion that is released by hydrolysis and then the resultant "second prodrug" is released (p 5, ln 22 – 25). The compounds have the following formula where in the variables are as defined on p 3, ln 17 - p 4, ln 25.

(I) 

R_{11} is a polymer such as an alkylene oxide and G can be – carbon double bonded to Y_1 and B, wherein B can be a residue of an enzyme or protein (p 5, ln 11 – 12), which reads on the amine-containing biologically active drug of the instant claims. The Ar moiety can be either a monocyclic or a dicyclic aromatic hydrocarbon or aromatic heterocycle with 5 or 6 atoms in the ring (p 8, ln 15 - p 10, ln 2). L_1 is a bifunctional linker that can contain Q (p 3, ln 19) that can act as a nucleophile due to the presence

of free electron pair that assist in hydrolysis of the chain (p 12, ln 27 – p 13, ln 13). The double prodrugs are unique in that the polymeric portion is first released by hydrolysis and the resultant “second prodrug” undergoes a 1,4 or 1,6-aryl or benzyl elimination to regenerate the amine containing bioactive compound (p 5, ln 22 – 25). The linkage between the polymer and the “second” prodrug hydrolyses at a rate which allows the compound to retain its enhanced solubility and circulating half-life (p 5, ln 26 – p 6, ln 6). Polyethylene glycol is a preferred substantially non-antigenic polymer (p 15, ln, 10 – 11) that is functionalized for attachment to the linkage via M, X or Q (p 15, ln 22 – p 16, ln 1). Molecular weights for the polymer of between 5,000 to about 40,000 are particularly preferred and must have a mass high enough to provide sufficient circulation of the double prodrug before hydrolysis of the linker (p 16, ln 17 – 28). The proteins or peptides will have at least one amino group for polymer attachment (p 23, ln 14 onward). These conjugates can be prepared by reaction of a thiazolidinyl thione- or succinimidyl carbonate-activated PEG as the activated polymer with a benzyl-elimination-based double prodrug (p 30, ln 8 – p 31, ln 25). The activating moiety can also include a spacer moiety located proximal to the polymer (p 31, ln 26 – 27). In figure 1, a compound containing a drug linked via a carbamate linkage to an intervening segment (the carrier of the present claims) and a polymer (R_{11}) is prepared.

Claim 95 is a product-by-process claim that indicates that recombinant DNA technology was used to prepare this protein. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of

production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) **MPEP 2113**. As recombinant DNA is technology is used as way to prepare large amount of peptides or proteins without the need to isolate them from cells or tissues and not to alter the material which is made, the product produced is the same.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

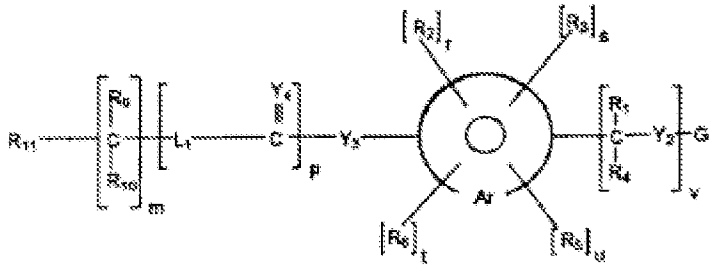
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 89 – 93, 95, 99, 101, 102, 115, 116, 118 - 120 and 122 – 124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenwald et al. (WO 99/30727) in view of Amir et al. (Angew Chem Int. Ed., 2003), Finn et al. (US 2004/0038892) and Veronese (Biomaterials, 2001).

Greenwald et al. discloses double prodrugs with a polymeric portion that is released by hydrolysis and then the resultant "second prodrug" is released (p 5, ln 22 – 25). The compounds have the following formula where in the variables are as defined

(I) 

on p 3, ln 17 - p 4, ln 25.

R_{11} is a polymer such as an alkylene oxide and G can be – carbon double bonded to Y_1 and B, wherein B can be a residue of an enzyme or protein (p 5, ln 11 – 12), which reads on the amine-containing biologically active drug of the instant claims. The Ar moiety can be either a monocyclic or a dicyclic aromatic hydrocarbon or aromatic

heterocycle with 5 or 6 atoms in the ring (p 8, ln 15 - p 10, ln 2). L_1 is a bifunctional linker that can contain Q (p 3, ln 19) that can act as a nucleophile due to the presence of free electron pair that assist in hydrolysis of the chain (p 12, ln 27 – p 13, ln 13). The double prodrugs are unique in that the polymeric portion is first released by hydrolysis and the resultant "second prodrug" undergoes a 1,4 or 1,6-aryl or benzyl elimination to regenerate the amine containing bioactive compound (p 5, ln 22 – 25). The linkage between the polymer and the "second" prodrug hydrolyses at a rate which allows the compound to retain its enhanced solubility and circulating half-life (p 5, ln 26 – p 6, ln 6). Polyethylene glycol is a preferred substantially non-antigenic polymer (p 15, ln, 10 – 11) that is functionalized for attachment to the linkage via M, X or Q (p 15, ln 22 – p 16, ln 1). Molecular weights for the polymer of between 5,000 to about 40,000 are particularly preferred and must have a mass high enough to provide sufficient circulation of the double prodrug before hydrolysis of the linker (p 16, ln 17 – 28). The proteins or peptides will have at least one amino group for polymer attachment (p 23, ln 14 onward). These conjugates can be prepared by reaction of a thiazolidinyl thione- or succinimidyl carbonate-activated PEG as the activated polymer with a benzyl-elimination-based double prodrug (p 30, ln 8 – p 31, ln 25). The activating moiety can also include a spacer moiety located proximal to the polymer (p 31, ln 26 – 27). In figure 1, a compound containing a drug linked via a carbamate linkage to an intervening segment (the carrier of the present claims) and a polymer (R_{11}) is prepared.

Greenwald et al. does not disclose the multiple carbamate linkages in the same compound or rHGH.

Amir et al. discloses a trigger and functional molecules are joined together by use of a carbamate containing 'adapter' (p 4494, col 1, ¶ 3 and p 4495, figure 1). The adapter is based on 2,6-bis(hydroxymethyl)-*p*-cresol and the reporter molecules are attached via carbamate linkages (p 4495, col 1, ¶ 2 and scheme 1). Self-immolation of the backbone occurs through a spontaneous chain reaction with cyclization and 1,4-quinone methide rearrangement (scheme 1 legend).

Finn et al. discloses human growth hormone is a 191 amino acid polypeptide (¶P [0006]) and a recombinant version has been available commercially for several years (¶ [0003]). Chemical modification with a water-soluble polymer in order to decrease the clearance rate, improve stability or abolish antigenicity has been proposed (¶ [0009]). Notably, poly(ethylene glycol) has been used in the preparation of therapeutic protein products (¶ [0009]). PEGylated HGH using a succinimidyl ester of carboxymethylated PEG (mPEG-NHS-5000) selectively conjugated to primary amines has been reported (¶ [0020]). Finn et al. describes PEG covalently bound through amino acid residues of the hGH with the PEG more preferably having a molecular weight between 5,000 and about 40,000 (¶¶ [0044], [0046]). This linkage is accomplished via a terminal reactive group, which may or may not leave a linking moiety (spacer) between the PEG and the protein (¶ [0048]). Mercapto groups, if available on the hGH, can be used as attachment sites for suitably activate polymers such as maleimides (¶ [0052]). In another preferred aspect, carbamate (urethane) linkages are formed between with protein amino group (¶ [0059]). Double prodrugs (like those disclosed by Greenwald et al.) can be prepared to

produce a sustained release form of HGH in which the PEG and HGH are attached via a functional linker that can predictably break down to release free HGH (¶ [0060]).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate multiple carbamate linkers and HGH in the double prodrugs of Greenwald et al. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because Finn et al. disclose PEG-HGH conjugates with possibly intervening linkage sequences that provide for the controlled release of HGH. The carbamates and benzene ring containing linkers of Amir et al. allow for the required elimination behavior through a self-immolating linker of these double prodrugs. Selection of the activity of the active moiety depends on the desired action of the prepared conjugate.

None of the references disclose why a linkage through a sulfur atom with PEG-maleimide would be useful.

Veronese discloses a wide variety of methods by which peptides and proteins can be PEGylated. Section 7 (p 410) discussed that cysteines are generally rare residue but offers the opportunity for site-directed PEGylation (p 410, col 1, ¶ 2).PEG-maleimide (figure 9 b1) will react with a thiol to form a PEG-conjugate at that location (third line of figure 9, p 410). This reagent reacts with the sulfhydryl group at neutral or mild alkaline conditions and any reaction with amino groups has significantly lower kinetics if the pH is increased (sentence bridging cols 1 and 2 on p 410).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to incorporate an S-succinimido (maleimide) linkage to PEG into

the double prodrugs of Greenwald and Finn. The person of ordinary skill in the art would have been motivated to make those modifications and reasonably would have expected success because the use of an amino conjugation reaction (resulting in carbamate formation) and PEG-maleimide coupling reaction through a sulfhydryl group will allow for the consistent formation of double prodrugs due to the decreased reactivity of the PEG-maleimide with any amino groups that might be present.

Claim 95 is a product-by-process claim that indicates that recombinant DNA technology was used to prepare this protein. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) **MPEP 2113**. As recombinant DNA is technology is used as way to prepare large amount of peptides or proteins without the need to isolate them from cells or tissues and not to alter the material which is made, the product produced is the same.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 89 - 93, 95, 99, 1010, 102, 115, 116, 118 – 120 and 122 - 124 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting

as being unpatentable over claims 32 - 54 of copending Application No. 12/663628. Although the conflicting claims are not identical, they are not patentably distinct from each other because the polymeric compounds of US'628 are encompassed by the present claims.

The claims of US'628 recite compounds having the formula (polymer)-(releasing linked capable of undergoing autohydrolysis)-(exendin or exendin agonist). This corresponds to the formula in instant claims 89 or masking group- carrier – activity moiety. The formulas set forth in claims 40 and 41 of US'628 are more specific then the formulas set forth in instant claim 90 and several variables in the instant formulas have a single defined value in the claims of US'628. Thus the claims of the two applications are not patentably distinguished from each other as the same compounds are claimed by both applications.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 89 - 93, 95, 99, 1010, 102, 115, 116, 118 – 120 and 122 - 124 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 35 of copending Application No. 12/865693. Although the conflicting claims are not identical, they are not patentably distinct from each other because the same compounds are encompassed by the present claims and the claims of US'693.

The instant claims are drawn to masking group – carrier – activity moiety. The activity moiety corresponds to the D in the D-L prodrugs claimed in US'693 that is a nitrogen containing biologically active moiety. The L of US'693 is a non-biologically active linker moiety L^1, corresponding to the carrier section of the compounds of the instant claims. L^1 is substituted with one to four L^2-Z groups, wherein Z is a carrier group such as polymer (claims 23 and 24) or protein (claim 25), corresponding to the masking group of the present claims. The linker can contain pairs of variables that are joined together to form rings such as the aromatic ring such as phenyl so compounds falling within the scope of the formulas of instant claim 90 are disclosed and claimed by the US'693 application.

This is a provisional obviousness-type double patenting rejection.

14. Claims 89 - 93, 95, 99, 101, 102, 115, 116, 118 – 120 and 122 - 124 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 - 36 of copending Application No. 12/990101. The recombinant HGH PEGylated prodrug conjugates of US'101 fall within the scope of the compounds claimed by the present claims. The HGH is the activity moiety, the self-hydrolysable transient linker is the carrier and the PEG is the masking group. Compounds such as those recited in claims 36 fall within the scope of the compounds of instant claim 90. Thus the claims of the two applications are not patentably distinguished from each other as the same compounds are claimed by both applications.

This is a provisional obviousness-type double patenting rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NISSA WESTERBERG whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nissa M Westerberg/
Primary Examiner, Art Unit 1618